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id KAA23805 for <mary>; Wed, 4 Jun 1997 10:28:43 -0400 (EDT)
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To: mary@rockvax.rockefeller.edu
Subject: hcc: fax =/=> Gordon Ringold, Affymax [Super-Taq; lysozyme] ✓6/4/97
Date: Wed, 04 Jun 1997 10:28:59 EDT
From: Joshua Lederberg <jsl@rockvax.rockefeller.edu> 415-424-8312 ft

Dear Gordon

I had a great talk with Alex; it is wonderful to see both of you so enthusiastic.

I had a thought about objectives for enzyme improvement. It may actually have a significant market, though not to be compared with a pharma -- actually let me start with that first:

a. Ultra-lysozyme, a modification of human lysozyme (like tears) to be used as a topical antibiotic and food preservative. Probably produce it in yeast, which should not be vulnerable. It takes special adjuncts to attack gram-negatives. But even against gram-pos, like staph, it could do a lot in wound infections (say on bandaids). P&G might sponsor it for mouthwash. ***

b. Super-Taq: a DNA polymerase with enhanced fidelity and processivity, no harm if it's a bit slower, for many applications now limited by those parameters. Develop it in the context of a fragment lacking the editting exonuclease, so the whole burden of fidelity was on the polymerase. Some work bearing on this has been done in the context of drug-resistant HIV reverse-transcriptase. You might want to get Tom Kunkel for the advisory board. **

Would Roche sponsor the effort?

I'd bet Dave Thaler could set up a selective system where infidelity really imposed a severe penalty: e.g. a conditional dominant lethal turned on by SOS system in E. coli.

c. Muta-Taq: the opposite, to facilitate scrambling a DNA interval. Might be a marginal improvement over existing tricks. Some analogue of terminal deoxynucleotide transferase (nature's gimmick to get random assembly). I don't know if Pim has looked at 'rag', likewise the recombinases that shuffle DNA for antibody diversification.

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I did some lit-scan on "random mutagenesis" etc., and did not see much any more exciting than above.

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Authors
Boyer JC. Bebenek K. Kunkel TA.**
Institution
Laboratory of Molecular Genetics, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.
Title
Analyzing the fidelity of reverse transcription and transcription.
Source
Methods in Enzymology. 275:523-37, 1996.

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Albeit, the literature is not very encouraging, but perhaps not the last word. And gingivitis may be more to the point than caries. There were some trials (papers in Japanese) with dentrifice containing natural, not enhanced, lysozyme.

Authors
Stuchell RN. Mandel ID.
Title
A comparative study of salivary lysozyme in caries-resistant and caries-susceptible adults.
Source
Journal of Dental Research. 62(5):552-4, 1983 May.
Abstract
Lysozyme concentration was quantitated immunochemically in parotid and submandibular-sublingual saliva of 46 caries-resistant and 17 caries-susceptible adults. There was essentially no difference between the two groups. The concentration of lysozyme was three times higher in the submandibular-sublingual than in the parotid secretion, and was significantly higher in unstimulated submandibular saliva than in secretions stimulated with 1, 2, or 4% citric acid. There were no significant differences in flow rate between caries-resistant and -susceptible subjects. Salivary lysozyme concentration is not a critical determinant of resistance or susceptibility to caries.